REMARKS/ARGUMENTS

Claims 1-10, 13-16, 26 and 28-32 are pending in this application. Claims 1-10, 13-16, 26 and 28-30 have been rejected under 35 U.S.C. §102(e) and claims 31 and 32 have been rejected under 35 U.S.C. §103(a). For the reasons set forth below, Applicant respectfully traverses these grounds of rejection. No claims are amended, added or canceled by the present Response.

Rejections Under 35 U.S.C. §102(e)

Claims 1-10, 13-16, 26 and 28-30 have been rejected under 35 U.S.C. §102(e) based on U.S. Pat. No. 5,846,533 by Prusiner *et al.* ("the "Prusiner '533 patent"). In particular, the Office Action states:

> Prusiner *et al.* teach a method for typing a sample of a prion or spongiform encephalopathy disease or Creutzfeldt-Jakob disease, the method comprising comparing and identifying similar physicochemical properties of the sample with a standard sample of known type (Abstract and Figures 8, 11 and 12 and Example 15 and Column 5, lines 45-62).

Respectfully, Applicant must disagree with this description of the teachings of the Prusiner '533 patent.

First and foremost, the methods described in the Prusiner '533 patent are used to produce and identify *antibodies* and are not methods for typing a sample of prion or spongiform encephalopathy disease or Creutzfeldt-Jakob disease by comparing or identifying *physicochemical properties*, including the *sizes* and *ratios* of *glycoforms*. In addition, the methods of the Prusiner '533 patent are used only to produce and identify antibodies that are able to recognize specific PrP^{Sc} *isoforms* - not *glycoforms*. The terms "isoform" and "glycoform" are not equivalent and, therefore, the teachings of the Prusiner '533 patent are generally not relevant to the present invention.

Specifically, and contrary to the assertion in the Office Action, nothing in the Abstract teaches a "method for typing a sample of a prion or spongiform encephalopathy disease [by] comparing and identifying similar physicochemical properties of the sample with a standard

sample of known PrP^{sc} type, wherein the *physicochemical properties* are the *sizes* and *ratios* of distinct PrP^{sc} *glycoforms*" (emphasis added). Furthermore, nothing in Figures, 8, 11 or 12, or the descriptions or discussions of those figures, teaches anything whatsoever about such methods of typing samples by "comparing and identifying similar *physicochemical properties*" which are "the *sizes* and *ratios* of distinct PrP^{sc} *glycoforms*" (emphasis added). Rather, the Abstract and the cited figures simply relate to the use of PrP^{Sc} antibodies which are specific for certain *isoforms*. The antibodies are not, however, *glycoform*-specific, and there is no teaching of comparing the relative sizes and ratios of such glycoforms.

Thus, Figure 8 shows histoblots that provide no information on the presence of different *glycoforms* of PrP^{Sc}. Rather, the histoblots merely demonstrate that the test antibody recognizes molecules present in the brain section and show the distribution of the molecules within the brain. Figure 11 shows the results of an assay designed to show only that the antibody is useful in binding to the molecule against which it has been raised (see column 38, lines 35-38). Finally, Figure 12 shows binding using different recombinant antibody fragments and identifies the best antibody fragment for such binding. There is absolutely no teaching in the Abstract or cited figures regarding comparing and identifying similar physicochemical properties (*e.g.*, relative sizes and ratios of glycoforms) of the sample with a standard sample of known type.

Next, the Office Action suggests that Example 15 of the Prusiner '533 patent is particularly relevant. In particular, the Office Action suggests that Example 15 somehow shows "a method for assessing and predicting the susceptibility of a human to bovine spongiform encephalopathy or a derivative thereof." Example 15, however, relates to histoblots of cryostat sections of brains from normal and scrapie-infected mice using PrP-specific antibodies. Again, there is no teaching whatsoever relating to methods of typing samples by "comparing and identifying similar physicochemical properties" which are "the *sizes* and *ratios* of distinct PrP^{sc} *glycoforms*" (emphasis added). In addition, because the example relates to histoblots, there is no teaching regarding the sizes or ratios of *any* PrP proteins. More fundamentally, however, because the example relates to histoblots of frozen brain sections, it is inconceivable how this method could be used to "assess[ ] and predict[ ] the susceptibility of a human to bovine

spongiform encephalopathy" without removing the unfortunate human's brain. Rather, Example 15 merely describes a positive control experiment that demonstrates that the antibody of the Prusiner '533 patent recognizes the Syrian hamster PrP 27-30 protein in brains from mice inoculated with that protein.

Next, the Office Action suggests that Example 13 and Figures 11 and 12 teach "the sizes and ratios of distinct PrP^{sc} glycoforms." Respectfully, Applicant must again disagree. The Prusiner '533 patent does not refer to different *glycoforms* but, instead, always refers to *isoforms* of the PrP^{sc} molecule. Indeed, the Prusiner '533 patent teaches away from investigating different glycoforms at column 12, lines 63-67, where it states:

> To date, attempts to identify any post-translational chemical modifications in PrP^{c} that lead to its conversion to PrP^{Sc} have proven fruitless (Stahl, et al 1993 *Biochemistry*). Consequently, it has been proposed that PrP^{c} and PrP^{Sc} are in fact conformational isomers of the same molecule.

Because glycoforms are variants of a protein which result from differences in a post-translational modification (*i.e.*, glycosylation), Applicant submits that the Prusiner '533 patent clearly teaches away from methods based on the analysis of physicochemical properties of different glycoforms.

Moreover, Example 13 relates to the selection of phage particles expressing anti-PrP antibodies specific for *isoforms* of PrP^{Sc}. Specifically, the example discloses that a phage display antibody library was prepared from lymphocyte RNA of a mouse immunized with a specific PrP^{Sc} *isoform*. The phage were selected for their ability to bind only one specific PrP^{Sc} *isoform*. The immunoreactivity of the selected phage or isolated antibody was then tested for positive reactivity with PrP^{Sc} *isoforms*, not *glycoforms*, and for cross-reactivity with PrP^{c}. Consequently, Example 13 of the Prusiner '533 patent does not teach methods of comparing and identifying the sizes and ratios of distinct PrP^{Sc} *glycoforms*. Figures 11 and 12, for reasons discussed above, also do not teach such methods.

Next, the Office Action suggests that Examples 8, 13 and 15 teach "a method for typing a sample for prion or spongiform encephalopathy disease, the method comprising comparing and identifying similar physicochemical properties of the sample with a standard sample of known type." Respectfully, as noted above, Applicant submits that the Prusiner '533 patent does not teach any such methods. Rather, the patent teaches methods of producing and identifying *antibodies* that specifically bind to a PrP^{Sc} *isoform*.

As discussed above, Example 13 relates to the preparation of a phage display library and the selection of a phage expressing an antibody that specifically binds to a PrP^{Sc} isoform. In addition, as discussed above, Example 15 relates to histoblots of cryostat sections of brains from normal and scrapie-infected mice using PrP-specific antibodies. These examples clearly do not teach the claimed methods. Example 8, which discloses the methods used by Prusiner *et al.* to disrupt rodent brain tissue and to prepare samples for SDS/PAGE and immunoblotting, does nothing to provide these teachings.

The Office Action next asserts that the Prusiner '533 patent teaches "a method wherein the comparison of physicochemical properties comprises a comparison of protease resistance," and cites to Example 15, column 36, lines 20-37, and column 12, lines 43-67.

As explained above, however, Example 15 of the Prusiner '533 patent relates to using in *histoblots*. The fact that the histoblots were, in some cases, treated with proteinase K to remove PrP^{c} proteins is *not*, however, equivalent to teaching a method of "comparing and identifying similar physicochemical properties of the sample with a standard sample of known PrP^{Sc} type, wherein the physicochemical properties are the *sizes* and *ratios* of distinct PrP^{sc} *glycoforms*" (as in claim 1) or "identifying that [the] prion protein can be characterized by having three distinct bands on an electrophoresis gel following proteinase K digestion, the bands comprising i) a band of highest molecular weight in the greatest proportion, ii) a band of lowest molecular weight in the lowest proportion, and iii) a band with a molecular weight between i and ii and a proportion between i and ii or characterized by having substantially similar glycoform proportions as bovine

spongiform encephalopathy" (as in claim 13). Rather, Prusiner *et al.* merely used proteinase K "to remove PrP^c" from the brain sections before histoblotting (column 36, lines 39-42).

As for the other portion of the specification cited to by the Office Action (column 12, lines 43-67), that passage merely provides a general teaching regarding the relation between the PrP^c and PrP^{Sc} proteins and, in fact, teaches away from the present invention. Specifically, the cited passage teaches that "[b]y using proteinase K it is possible to denature PrP^c but not PrP^{Sc}," that "[t]o date, attempts to identify any post-translational chemical modifications in PrP^c that lead to its conversion to PrP^{Sc} have proven fruitless," and that "[c]onsequently, it has been proposed that PrP^c and PrP^{Sc} are in fact conformational isomers of the same molecule" (column 12, lines 61-67). Thus, if anything, there is a teaching that PrP^c and PrP^{Sc} can be distinguished *not* by different *ratios* of different *size* bands following proteinase K treatment but, rather, by the *denaturation* of one form but not the other by proteinase K. Moreoever, the cited passage teaches away from the present invention's analysis of the different *glycoforms* that result from post-translational modification of glycosylation.

Finally, the Office Action suggests that Figure 11, lanes 9, 11 and 14, and Figure 12, lanes 4, 6, 7, 8 and 12, of the Prusiner '533 patent teach "a method for identifying infection in an animal and tissue of bovine spongiform encephalopathy . . . comprising isolating a prion protein from the animal and/or tissue and identifying that the prion protein can be characterized by having three distinct bands on an electrophoresis gel following proteinase K digestion," the bands comprising (i) a band of highest molecular weight in the greatest proportion, (ii) a band of lowest molecular weight in the lowest proportion, and (iii) a band with a molecular weight between (i) and (ii) and a proportion between (i) and (ii). Respectfully, Applicant must disagree.

Figure 11 shows that different recombinant Fab antibody fragments developed by Prusiner *et al.* were reactive against the Syrian hamster PrP 27-30 protein. The sole importance of the experiment is to show that different degrees of immunoprecipitation are obtained with different antibodies. Thus, the gel of Figure 11 merely demonstrates that the antibodies were differentially able to recognize the Syrian hamster PrP 27-30 molecule against which they were

raised. No importance was placed on the band pattern shown in the gel and the only comment the authors made was that the photo clearly shows higher degrees of immunoprecipitation when using the recombinant antibodies of the invention (column 38, lines 35-38).

Figure 12 shows the higher degree of immunoprecipitation achieved using antibodies 2R and 4D when compared to the 3F4 antibody (column 38, line 50-52). No importance is placed on the sizes and ratios of the bands. The gel of Figure 12 merely shows the recognition of a protein by an antibody raised against the protein and does not represent a method for identifying infection.

The Examiner is asked to consider the bands in lanes 5, 9 and 13 in Figure 12. These are the negative control bands and clearly show a highest molecular weight band and a middle molecular weight band. If lanes 4 and 5 are compared, it is clear that the antibody only specifically recognizes the new, lowest molecular weight band which appears between 29 and 33kDa in lane 4. The other bands in lane 4 (at 49 and 105kDa) are also present in the negative control of lane 5, and therefore cannot represent specific binding by the antibody.

Therefore, Applicant respectfully submits that there is no disclosure in the Prusiner '533 patent of a method for identifying infection by isolating a prion protein and identifying that the prion protein can be characterized by having three distinct bands on an electrophresis gel following proteinase K digestion, the bands comprising (i) a band of highest molecular weight in the greatest proportion, (ii) a band of lowest molecular weight in the lowest proportion, and (iii) a band with a molecular weight between (i) and (ii) and of a proportion between (i) and (ii), as described in claim 13.

For the foregoing reasons, Applicant submits that the Prusiner '533 patent does not anticipate the methods of claims 1-10, 13-16, 26 and 28-30, because the reference does not teach every element of the claimed invention. Therefore, Applicant respectfully requests that the rejections based upon the Prusiner '533 patent be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §103(a)

Claims 31 and 32 have been rejected under 35 U.S.C. §103(a) as being obvious over the Prusiner '533 patent in view of the Race *et al.* reference. Claims 31 and 32 depend from claims 9 and 16, respectively, adding only the limitation that the "prion is derived from a tissue of the lymphoreticular system selected from the group consisting of spleen, tonsil, or lymph node." Presumably, then, the Race *et al.* reference is cited only for its teachings regarding the presence of prions in the spleens and lymph nodes of scrapie-positive sheep.

For the reasons explained in detail above, Applicant submits that the Prusiner '533 patent does not teach the methods of claims 9 and 16. The Race *et al.* reference clearly does not teach the methods of claims 9 and 16.

Therefore, for the reasons stated above in connection with the rejections under 35 U.S.C. §102(e), Applicant submits that the combination of the Prusiner '533 patent and the Race *et al.* reference does not render obvious the methods of claims 31 and 32 under 35 U.S.C. §103(a) because the combined references do not teach or suggest every element of the claimed invention. Therefore, Applicant respectfully requests that the rejections based upon the Prusiner '533 patent and Race *et al.* reference be reconsidered and withdrawn.

SUMMARY

Claims 1-10, 13-16, 26 and 28-32 remain pending in the application. No claims are amended, added or canceled by the present Response.

Applicant requests that the Examiner reconsider the application and claims in light of the foregoing Response, and respectfully submits that the claims are in condition for allowance. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Applicant believes that no additional fees are required with the submission of present Response. However, in the event that any additional fees are necessary to maintain the pendency of the application, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 08-0219.

Respectfully submitted,
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